REMARKS

Claims 1-18, 20, 21, 23, 24 and 33-55 are pending in the application and are the subject of the instant office action.

Claims 11 and 12 have been amended to recite an independent claim format. As the amendments to both claims merely incorporate language of those claims from which they already depended, it is believed that the amendments do not narrow the scope of either claim but merely re-format claims 11 and 12 into independent claims.

In the office action, the Examiner noted an inconsistency regarding the designation(s) used in the specification for the 1H5 antibody. The undersigned would like to thank the Examiner for identifying this inconsistency and bringing it to Applicants' attention. Applicants' disclosure relates to an anti-DR4 antibody called "1H5.24.9". The reference to antibody "1H5.25.9" in the specification is an inadvertent typographical error. Applicants have amended the text on pages 8, 16, 17,and 35 to correct this error in the specification.

For the Examiner's convenience, a clean copy of the text of the (amended) paragraphs in the specification and now pending claims 1-18, 20, 21, 23, 24 and 33-35 are provided above. The amendments are illustrated in the attached pages entitled "Marked Up Version To Show Changes Made".

Section 112 Rejections

Claim 12 was rejected under Section 112, second paragraph, as being indefinite. Claim 12 has been amended herein to correct the inadvertent typographical error by Applicant in omitting the verb "binds" to section (c) of the claim when it was originally filed (it is readily apparent that the term "binds" had been correctly included in sections (a) and (b)). The term "binds" has been added to section (c) of claim 12 for purposes of correcting this error by Applicant.

Section 103 Rejections

Claims 1-5, 9, 10, 20, 21, 23, 24, 33, 34, 38-40, 42, 43, 47, 48 and 52-54 were rejected under Section 103(a) as being obvious over Pan et al. in view of Campbell. Claims 1-10, 20, 21, 23, 24, 33, 34, 36-43, 45-48

and 50-55 were also rejected under Section 103(a) as being obvious over Pan et al. in view of Campbell and Gussow et al. Claims 35, 44 and 49 were rejected under Section 103(c) as being obvious over Pan et al. in view of Campbell and further in view of Janeway et al. Applicants respectfully traverse these rejections.

None of these cited references teach or suggest the claimed invention. The Campbell, Gussow et al., and Janeway et al. references may relate to certain aspects of techniques for making monoclonals or human or chimeric antibodies (in a generic manner), but none of these references fill the void left by the Pan et al. reference. Pan et al. does not provide sufficient guidance to one skilled in the art to produce the claimed anti-DR4 antibodies. Applicants particularly wish to point out that the claimed DR4 antibodies of claims 33, 42 or 47 are not obvious over the cited references. Even assuming, for argument sake only (and without acquiescence to any assertions made by the Examiner), that an antibody to DR4 could be made using routine skill once a DNA or amino acid sequence structure of the DR4 receptor was available, the species of DR4 antibodies as claimed in claim 33 (i.e., an agonist antibody having apoptotic activity in a cancer cell(s)), claim 42 (i.e., a blocking antibody which blocks binding of Apo-2 ligand to DR4), or claim 47 (i.e., a blocking antibody that blocks binding of Apo-2 ligand induced apoptosis in a cancer cell(s)) would not be expected. Until such types of antibodies are made and characterized, the antibodies are not known or expected. Pan et al. does not disclose anything about DR4 antibodies or properties of DR4 antibodies. Accordingly, the combination of teachings of Pan et al. with the other references cited by the Examiner fails to render the Applicants' claims obvious. Withdrawal of the Section 103(a) rejections is therefore requested.

Information Disclosure Statement

Applicants wish to note that an Information Disclosure Statement and Form 1449 were filed on February 12, 2002 (after the issuance of the instant office action). It would be appreciated if the Examiner could return the initialed Form 1449 to Applicants with the next office communication to indicate that the Examiner has received and considered

the information cited therein.

Respectfully submitted,
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MARKED UP VERSION TO SHOW CHANGES MADE

IN THE SPECIFICATION:

On page 8, in the paragraph on lines 8-11, the text has been amended as follows:

--- Figure 8A shows graphs illustrating percent (%) apoptosis (as determined by FACS analysis) induced in 9D cells by various concentrations of DR4 antibodies [1H5.25.9] 1H5.24.9 ("1H5"), 4G7.18.8 ("4G7"), and 5G11, in the absence or presence of goat anti-mouse IgG Fc or rabbit complement.---

On page 16, lines 34-41 - page 17, lines 1-18, the text has been amended as follows:

----As described in the Examples below, various anti-DR4 monoclonal antibodies have been identified and prepared. Certain of those antibodies, referred to as 4E7.24.3, 4H6.17.8, [1H5.25.9] 1H5.24.9, 4G7.18.8, and 5G11.17.1 herein, have been deposited with ATCC. In one embodiment, the monoclonal antibodies of the invention will have the same biological characteristics as the monoclonal antibodies secreted by the hybridoma cell line(s) referred to above which have been deposited with ATCC. The term "biological characteristics" is used to refer to the *in vitro* and/or *in vivo* activities or properties of the monoclonal antibody, such as the ability to specifically bind to DR4 or to block, induce or enhance DR4 activation (or DR4-related activities). As disclosed in the present specification (see Figure 6), the monoclonal antibody 4E7.24.3 is characterized as specifically binding to DR4 (and having some cross reactivity to Apo-2, DcR1 or DcR2), capable of inducing apoptosis, and not capable of blocking DR4. The monoclonal antibody 4H6.17.8 is characterized as specifically binding to DR4 (and having some cross-reactivity to Apo-2, DcR1 or DcR2), capable of inducing apoptosis, and capable of blocking Apo-2 ligand binding to DR4. The properties and activities of the [1H5.25.9] 1H5.24.9, 4G7.18.8 and 5G11.17.1 antibodies are described in the Examples below (and also referred to in Fig. 17). Optionally, the monoclonal antibodies of the present invention will bind to the same epitope(s) as the 4E7.24.3, 4H6.17.8, [1H5.25.9] 1H5.24.9, 4G7.18.8, and/or 5G11.17.1 antibodies disclosed herein.

This can be determined by conducting various assays, such as described herein and in the Examples. For instance, to determine whether a monoclonal antibody has the same specificity as the DR4 antibodies specifically referred to herein, one can compare its activity in DR4 blocking assays or apoptosis induction assays, such as those described in the Examples below.

On page 35, in the paragraph on lines 24-32, the text has been amended as follows:

--- The following materials have been deposited with the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia, USA (ATCC):

Material	ATCC Dep. No.	Deposit Date
4E7.24.3	HB-12454	Jan. 13, 1998
4H6.17.8	HB-12455	Jan. 13, 1998
[1H5.25.9] 1H5.24.9	HB-12695	April 1, 1999
4G7.18.8	PTA-99	May 21, 1999
5G11.17.1	HB-12694	April 1, 1999

IN THE CLAIMS:

11. (Amended) An isolated monoclonal antibody which specifically binds to DR4 polypeptide comprising amino acid residues 24 to 218 of Figure 1 (SEQ ID NO:1) [The antibody of Claim 4 having] and which has the same biological characteristics of (1) the monoclonal antibody produced by the hybridoma cell line deposited under American Type Culture Collection Accession Number ATCC HB-12695; (2) the monoclonal antibody produced by the hybridoma cell line deposited under American Type Culture Collection Accession Number ATCC HB-12694; or (3) the monoclonal antibody produced by the hybridoma cell line deposited under American Type Culture Collection Accession Number ATCC PTA-99.

12. (Amended) An isolated monoclonal antibody which specifically binds to DR4 polypeptide comprising amino acid residues 24 to 218 of Figure 1 (SEQ ID NO:1) [The antibody of Claim 4 wherein the antibody] and which

binds to the same epitope as (1) the epitope to which the monoclonal antibody produced by the hybridoma cell line deposited under American Type Culture Collection Accession Number ATCC HB-12695 binds; (2) the epitope to which the monoclonal antibody produced by the hybridoma cell line deposited under the American Type Culture Collection Accession Number ATCC HB-12694 binds; or (3) the epitope to which the monoclonal antibody produced by the hybridoma cell line deposited under American Type Culture Collection Accession Number ATCC PTA-99 binds.